

WHAT IS CLAIMED

*Sub B* 1. A preparation of replication defective recombinant retrovirus expressing human factor VIII protein, wherein said recombinant retrovirus is capable of infecting human cells and is resistant to degradation by human complement.

2. The recombinant retrovirus preparation of claim 1, wherein said recombinant retrovirus expresses a B domain-deleted form of factor VIII.

3. The recombinant retrovirus preparation of claim 2, wherein said B domain-deleted form of factor VIII is the SQN mutation.

*Sub C1* 4. The recombinant retrovirus preparation of claim 1, wherein said recombinant retrovirus preparation has a titer on HT1080 cells of greater than  $10^6$  cfu/ml.

5. The recombinant retrovirus of claim 4, wherein said retrovirus preparation has a titer on HT1080 cells of greater than  $10^7$  cfu/ml.

*Sub B3* 6. A preparation of replication defective recombinant retrovirus expressing human factor VIII protein, wherein said recombinant retrovirus preparation is resistant to degradation by human complement and is capable of inducing long term systemic expression of human factor VIII when administered intravenously to a human afflicted with hemophilia A, wherein said long term systemic expression results in a measurable level of recombinant human factor VIII protein being produced in the blood of said human for a period of at least 30 days after the administration of said recombinant retroviral vector preparation.

7. The recombinant retrovirus preparation of claim 6, wherein said recombinant retrovirus expresses a B domain-deleted form of factor VIII.

8. The recombinant retrovirus preparation of claim 7, wherein said B domain-deleted form of factor VIII is the SQN mutation.

9. The recombinant retrovirus preparation of claim 6, wherein said recombinant retrovirus preparation has a titer on HT1080 cells of greater than  $10^6$  cfu/ml.

10. The recombinant retrovirus of claim 9, wherein said retrovirus preparation has a titer on HT1080 cells of greater than  $10^7$  cfu/ml.

11. The recombinant retrovirus preparation of claim 6, wherein said long term systemic expression results in measurable levels of recombinant human factor VIII protein being produced in the blood of said human for a period of at least six months after the administration of said recombinant retroviral vector.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a replication defective recombinant retrovirus expressing human factor VIII protein, wherein said recombinant retrovirus is capable of infecting human cells and is resistant to degradation by human complement.

13. The pharmaceutical composition of claim 12, wherein said recombinant retrovirus expresses a B domain-deleted form of factor VIII.

14. The pharmaceutical composition of claim 13, wherein said B domain-deleted form of factor VIII is the SQN mutation.

15. The pharmaceutical composition of claim 12, wherein said recombinant retrovirus preparation has a titer on HT1080 cells of greater than  $10^6$  cfu/ml.

16. The pharmaceutical composition of claim 15, wherein said retrovirus preparation has a titer on HT1080 cells of greater than  $10^7$  cfu/ml.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a replication defective recombinant retrovirus expressing human factor VIII protein, wherein said recombinant retrovirus is resistant to degradation by human complement and is capable of inducing long term systemic expression of human factor VIII when administered intravenously to a human afflicted with hemophilia A, wherein said long term systemic expression results in a measurable level of recombinant human factor VIII protein being produced in the blood of said human for a period of at least 30 days after the administration of said recombinant retrovirus.

18. The pharmaceutical composition of claim 17, wherein said recombinant retrovirus expresses a B domain-deleted form of factor VIII.

19. The pharmaceutical composition of claim 18, wherein said B domain-deleted form of factor VIII is the SQN mutation.

20. The pharmaceutical composition of claim 17, wherein said recombinant retrovirus preparation has a titer on HT1080 cells of greater than  $10^6$  cfu/ml.

21. The pharmaceutical composition of claim 20, wherein said retrovirus preparation has a titer on HT1080 cells of greater than  $10^7$  cfu/ml.

22. The pharmaceutical composition of claim 20, wherein said long term systemic expression results measurable levels of human factor VIII protein being produced in the blood of said human for a period of at least six months after the administration of said recombinant retroviral vector.

23. A method of administering a preparation of replication defective recombinant retrovirus expressing human factor VIII protein to a patient afflicted with hemophilia A comprising injecting said preparation of recombinant retrovirus into a blood vessel of said patient, wherein said recombinant retrovirus preparation is resistant to human complement and expresses human factor VIII protein in the blood of said patient resulting in a measurable level of human factor VIII protein being produced in said patient for a period of at least 30 days after the injection of said recombinant retrovirus preparation.

24. The method of claim 23, wherein said recombinant retrovirus expresses a B domain-deleted form of factor VIII.

25. The method of claim 24, wherein said B domain-deleted form of factor VIII is the SQN mutation.

26. The method of claim 23, wherein said recombinant retrovirus has a titer of greater than  $10^6$  on HT1080 cells.

27. The method of claim 26, wherein said retrovirus has a titer of greater than  $10^7$  on HT1080 cells.

28. The method of claim 23, wherein said long term systemic expression results in measurable levels of human factor VIII protein being produced in the blood of said human for a period of at least six months after the administration of said recombinant retroviral vector.

29. The method of claim 23 wherein said blood vessel is a peripheral vein.

30. ~~A method of infecting liver cells in vivo with a preparation of recombinant retrovirus expressing factor VIII protein comprising injecting said recombinant retrovirus preparation into a blood vessel of said patient, wherein said recombinant retrovirus preparation is resistant to degradation by human complement, and wherein the liver cells of said patient are infected with said recombinant retrovirus resulting in the production of recombinant factor VIII protein in said liver cells.~~

31. The method of claim 30, wherein said recombinant retrovirus expresses a B domain-deleted form of factor VIII.

32. The method of claim 31, wherein said B domain-deleted form of factor VIII is the SQN mutation.

33. The method of claim 30, wherein said recombinant retrovirus has a titer of greater than  $10^6$  on HT1080 cells.

34. The method of claim 33, wherein said retrovirus has a titer of greater than  $10^7$  on HT1080 cells.

35. The method of claim 30, wherein said long term systemic expression results in measurable levels of human factor VIII protein being produced in the blood of said human for a period of at least six months after the administration of said recombinant retroviral vector.

36. ~~The method of claim 30 wherein said blood vessel is a peripheral vein.~~

37. A TK-1 retroviral vector which expresses a factor VIII protein.

38. The retroviral vector of claim 37 wherein said factor VIII protein is a B-domain deleted factor VIII protein.

39. The retroviral vector of claim 38 wherein said B-domain deleted factor VIII protein is the factor VIII SQN deletion.

40. The retroviral vector of claim 39 wherein said factor VIII protein comprises the amino acid sequence depicted in Seq. ID No. 47.

41. The retroviral vector of claim 40 wherein said factor VIII protein is encoded by the nucleic acid sequence depicted in Seq. ID No. 46.

42. A retroviral vector which expresses a factor VIII protein, wherein said retroviral vector is selected from the group consisting of pBA-5a, pBA-5b and pBA-5c.

43. The retroviral vector of claim 42 wherein said factor VIII protein is a B-domain deleted factor VIII protein.

44. The retroviral vector of claim 43 wherein said B-domain deleted factor VIII protein is the factor VIII SQN deletion.

45. The retroviral vector of claim 44 wherein said factor VIII protein comprises the amino acid sequence depicted in Seq. ID No. 47.

46. The retroviral vector of claim 45 wherein said factor VIII protein is encoded by the nucleic acid sequence depicted in Seq. ID No. 46.

47. A pBA-9b retroviral vector which expresses a factor VIII protein.

48. The retroviral vector of claim 47 wherein said factor VIII protein is a B-domain deleted factor VIII protein.

49. The retroviral vector of claim 48 wherein said B-domain deleted factor VIII protein is the factor VIII SQN deletion.

50. The retroviral vector of claim 49 wherein said factor VIII protein comprises the amino acid sequence depicted in Seq. ID No. 47.

51. The retroviral vector of claim 50 wherein said factor VIII protein is encoded by the nucleic acid sequence depicted in Seq. ID No. 46.

52. A pBA-8b retroviral vector which expresses a factor VIII protein.

53. The retroviral vector of claim 52 wherein said factor VIII protein is a B-domain deleted factor VIII protein.

54. The retroviral vector of claim 53 wherein said B-domain deleted factor VIII protein is the factor VIII SQN deletion.

55. The retroviral vector of claim 54 wherein said factor VIII protein comprises the amino acid sequence depicted in Seq. ID No. 47.

56. The retroviral vector of claim 55 wherein said factor VIII protein is encoded by the nucleic acid sequence depicted in Seq. ID No. 46.

*Sub-β4* 57. A preparation of replication defective recombinant retrovirus expressing human factor IX protein, wherein said recombinant retrovirus is capable of infecting human cells and is resistant to degradation by human complement.

*Sub B5* 58. A preparation of replication defective recombinant retrovirus expressing human factor IX protein, wherein said recombinant retrovirus preparation is resistant to degradation by human complement and is capable of inducing long term systemic expression of human factor IX when administered intravenously to a human afflicted with hemophilia B, wherein said long term systemic expression results in a measurable level of recombinant human factor IX protein being produced in the blood of said human for a period of at least 30 days after the administration of said recombinant retroviral vector preparation.

59. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a replication defective recombinant retrovirus expressing human factor IX protein, wherein said recombinant retrovirus is resistant to degradation by human complement and is capable of inducing long term systemic expression of human factor IX when administered intravenously to a human afflicted with hemophilia B, wherein said long term systemic expression results in a measurable level of recombinant human factor IX protein being produced in the blood of said human for a period of at least 30 days after the administration of said recombinant retrovirus.

60. A method of administering a preparation of replication defective recombinant retrovirus expressing human factor IX protein to a patient afflicted with hemophilia B comprising injecting said preparation of recombinant retrovirus into a blood vessel of said patient, wherein said recombinant retrovirus preparation is resistant to human complement and expresses human factor IX protein into the blood of said patient resulting in a measurable level of human factor IX protein being produced in said patient for a period of at least 30 days after the injection of said recombinant retrovirus preparation

*Sub B6* 61. A preparation of replication defective recombinant retrovirus expressing a therapeutic protein, wherein said recombinant retrovirus preparation is resistant to degradation by human complement and is capable of inducing long term systemic expression of said therapeutic protein when administered intravenously to a human, wherein said long term systemic expression results in a measurable level said therapeutic protein being produced in the blood of said human for a period of at least 30 days after the administration of said recombinant retroviral vector preparation.

62. The recombinant retrovirus preparation of claim 61, wherein said recombinant retrovirus preparation has a titer on HT1080 cells of greater than  $10^6$  cfu/ml.

63. The recombinant retrovirus preparation of claim 62 wherein said retrovirus preparation has a titer on HT1080 cells of greater than  $10^7$  cfu/ml.

64. The recombinant retrovirus preparation of claim 61 wherein said therapeutic protein is a human clotting factor selected from the group consisting of factor V, antithrombin III, protein C, prothrombin, and thrombomodulin.

65. The recombinant retrovirus preparation of claim 61 wherein said therapeutic protein is an interferon-alpha.

66. The recombinant retrovirus preparation of claim 65 wherein said interferon-alpha is selected from the group consisting of interferon- $\alpha 2a$ , interferon- $\alpha 2b$ , and interferon- $\alpha 2c$ .

67. The recombinant retrovirus preparation of claim 61 wherein said therapeutic protein is the LDL receptor.

68. The recombinant retrovirus preparation of claim 61 wherein said therapeutic protein is human growth hormone.

69. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a replication defective recombinant retrovirus expressing a therapeutic protein, wherein said recombinant retrovirus preparation is resistant to degradation by human complement and is capable of inducing long term systemic expression of said therapeutic protein when administered intravenously to a human, wherein said long term systemic expression results in an measurable level said therapeutic protein being produced in the blood of said human for a period of at least 30 days after the administration of said recombinant retroviral vector preparation.

70. The pharmaceutical composition of claim 69, wherein said recombinant retrovirus preparation has a titer on HT1080 cells of greater than  $10^6$  cfu/ml.

71. The pharmaceutical composition of claim 70 wherein said retrovirus preparation has a titer on HT1080 cells of greater than  $10^7$  cfu/ml.

72. The pharmaceutical composition of claim 69 wherein said therapeutic protein is a human clotting factor selected from the group consisting of factor V, antithrombin III, protein C, prothrombin, and thrombomodulin.

73. The pharmaceutical composition of claim 69 wherein said therapeutic protein is an interferon-alpha.

74. The pharmaceutical composition of claim 73 wherein said interferon-alpha is selected from the group consisting of interferon- $\alpha$ 2a, interferon- $\alpha$ 2b, and interferon- $\alpha$ 2c.

75. The pharmaceutical composition of claim 69 wherein said therapeutic protein is the LDL receptor.

76. The pharmaceutical composition of claim 69 wherein said therapeutic protein is human growth hormone.

77. A method of administering a preparation of replication defective recombinant retrovirus expressing a therapeutic protein to a human patient comprising injecting said preparation of recombinant retrovirus into a blood vessel of said patient, wherein said recombinant retrovirus preparation is resistant to human complement and expresses the therapeutic protein in said patient resulting in a measurable level of human factor IX protein being produced in said patient for a period of at least 30 days after the injection of said recombinant retrovirus preparation.

78. The method of claim 77 wherein said recombinant retrovirus preparation has a titer on HT1080 cells of greater than  $10^6$  cfu/ml.

79. The method of claim 78 wherein said retrovirus preparation has a titer on HT1080 cells of greater than  $10^7$  cfu/ml.

80. The method of claim 77 wherein said therapeutic protein is a human clotting factor selected from the group consisting of factor V, antithrombin III, protein C, prothrombin, and thrombomodulin.

81. The method of claim 77 wherein said therapeutic protein is an interferon-alpha.

82. The method of claim 81 wherein said interferon-alpha is selected from the group consisting of interferon- $\alpha$ 2a, interferon- $\alpha$ 2b, and interferon- $\alpha$ 2c.

83. The method of claim 77 wherein said therapeutic protein is the LDL receptor.

84. The method of claim 77 wherein said therapeutic protein is human growth hormone.

85. A method of increasing the efficiency of infecting a mammalian cell with a recombinant retrovirus comprising:

- a) contacting said cell with a growth factor capable of stimulating division of said cell; and
- b) infecting said cell with a recombinant retrovirus.

86. The method of claim 85 wherein said growth factor is KGF.

87. A method of administering a gene delivery vehicle expressing a therapeutic protein to a patient suffering from arthritis comprising:

- a) preparing a solution of said gene delivery vehicle in a pharmaceutically acceptable carrier; and
- b) injecting said solution into a joint of said patient.

88. The method of claim 87 wherein said gene delivery vehicle is a retroviral vector.

89. The method of claim 87 wherein said therapeutic protein is an enzyme capable of converting a prodrug into a cytotoxic compound.

90. The method of claim 89 wherein said enzyme is herpes simplex thymidine kinase.